Theoretical Analysis of Fluoroglycine Conformers

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ABSTRACT: Seven different optimized conformers of α-fluoroglycine ($H_2NCHFCOOH$) were obtained from *ab initio* calculations. Some of these conformers are exceptionally stable compared to similar conformers of glycine. Conformers in which the lone pair of electrons on the nitrogen atom are antiperiplanar to the C—F bond are more stable than conformers that do not have such an arrangement. The stability difference between conformers with such an arrangement and conformers that have the lone pair of electrons synperiplanar to the C—F bond is about 27 kJ/mol (calculated at the MP2/6-31+G* level). Conformers that have the lone pair of electrons antiperiplanar to the C—F bond possess a longer C—F bond, a shorter C—N bond, and sp^2-like amino bond angles. For some conformers an unusual hydrogen bond involving the acidic carboxylic acid hydrogen and the electronegative fluorine atom is observed.
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Keywords: amino acid; fluoroglycine; *ab initio* calculations; hydrogen bond; conformations

Introduction

Theoretical calculations have been widely used to successfully determine the stability of different conformations of a fairly large number of amino acids.[1] Because of the small number of atoms present in glycine it has been the most studied amino acid by this method.[2] For glycine, *ab initio* studies have been used to show that conformer **Ia** (Fig. 1) is the most stable conformer, and it is 35.2 kJ/mol more stable than another conformer, conformer **VIa**.[3] The results of these theoretical studies closely reflect those obtained experimentally.[4] One factor that contributes to the stability of conformer **Ia** is the number of hydrogen bonds that are present: there is a bifurcated hydrogen bond involving the amino hydrogens and the carbonyl oxygen, and there is another hydrogen bond that involves the carboxylic acid hydrogen and the carbonyl group. Another factor that contributes to the stability of conformer **Ia** is the arrangement of the C—N and C=O bonds. It is known that for compounds of the type X—CH_2(C=O)Y, where X is a polar group and Y is an alkoxy group, the most stable conformation is one in which the C—X bond eclipses the carbonyl

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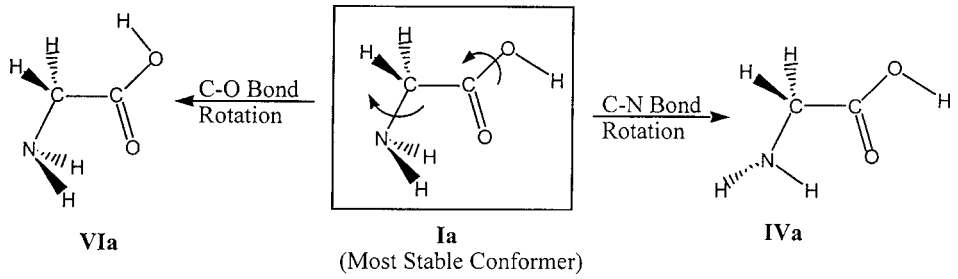

FIGURE 1. Three conformers of glycine. Conformer **IVa** is 7.1 kJ/mol less stable than conformer **Ia**, and conformer **VIa** is 35.2 kJ/mol less stable than conformer **Ia**.

bond.[5] A slight rotation about the glycine C—N bond of **Ia** results in conformer **IVa**, which is capable of the formation of only one hydrogen bond involving an amino hydrogen and the carbonyl oxygen, instead of a bifurcated hydrogen bond. As expected, **IVa** is less stable than **Ia** as shown in Figure 1. We were curious to find out if the substitution of one of the α-hydrogens of glycine with the electronegative fluorine would affect the relative stability of conformers similar to those shown in Figure 1.

Stabel et al. suggested that there is a very close isosteric relationship between fluorine and hydrogen.[6] As a result, the substitution of fluorine for hydrogen in peptides is often used to probe the effects that electronegative groups have on the activity of different substrates.[7] 4-Fluorothreonine is the only naturally occurring fluoroamino acid,[8] and it is known to have antimicrobial activity; its 4,4-difluoro and 4,4,4-trifluoro analogues have been shown to have antitumor and antifungal activity.[9] Incorporation of fluorinated amino acids into peptides gives analogues of ground-state and transition-state enzyme inhibitors, which have been shown to be useful chemotherapeutic agents.[10] Also, unnatural amino acids that have electronegative substituents in the α position, such as trifluoroalanine ($H_2NCH(CF_3)CO_2H$), are now routinely incorporated into proteins to induce specific protein activities.[11] Knowledge of the conformations that these amino acids adopt outside the protein gives an indication of the influence of the electronegative group on the conformation of proteins. The conformations that proteins adopt play an important role in the activity of the protein; some amino acids, such as proline, induce specific conformations in proteins, which in turn induce specific activity due to the conformation adopted.[12] In this study different conformers of α-fluoroglycine were examined by *ab initio* calculations to determine the stability of specific conformations and to determine the factors that contribute to the stability of these conformers.

Computational Methodology

The *ab initio* calculations were executed with Gaussian 94 using standard basis sets with no modification.[13] All low-level calculations were performed on our Silicon Graphics Indigo computer, and higher level calculations were performed at the San Diego Supercomputing Center. Conformations were optimized at each level of theory. Convergence was to the limits imposed internally by Gaussian 94. Vibrational frequencies were calculated at each level of theory, and the results were used to determine the nature of the structure (minima, saddle points, or second-order saddle points). All the conformations studied were minima at all the levels of theory we examined.

Results and Discussion

Table I shows the relative energies and the dipole moments of the different conformers of fluoroglycine considered, and Figure 2 shows the MP2 optimized geometries of the conformers that converged at that level. Table II shows the optimized geometrical parameters for those conformers. Three other conformations, **II'**, **III**, and **III'**, were analyzed that have N—C—C=O dihedral angles of 132.1°, −98.8°, and 114.0°, respectively. However, these conformations could be observed only at the RHF/6-31G* or RHF/6-311++G** level; when optimized using larger basis sets or levels of theory, **II'**, **III**, and **III'** converged to give **VI**, **IV**, and **V**, respectively.

It is obvious from Table I that the two most stable conformers (relative to conformer **I**) are **IV** and **V**, and **IV** is slightly more stable. As mentioned earlier,

TABLE I.
Relative Energies for Conformers of 2-Fluoroglycine (kJ/mol).

Conformer	Dipole Moment[a]	RHF/ 6-31G*	RHF/ 6-31+G*	RHF/ 6-311++G**	MP2/ 6-31+G*
I	3.1	0	0 (0)	0 (0)	0
II	5.9	1.9	4.0 (11.2)	4.7 (14.2)	1.2
IV	1.7	−13.7	−13.9 (7.4)	−12.6 (7.1)	−15.7
V	2.4	−13.9	−14.2 (10.9)	−12.8 (11.4)	−13.9
V′	4.7	7.3	7.7	7.5	12.0
VI	3.3	5.8	7.0 (37.4)	6.9 (35.2)	4.7
VII	4.4	3.9	5.1	5.2	0.6

The values in parentheses are relative energies for similar conformers of glycine.
[a] Calculated at HF/6-31+G*//MP2/6-31+G*.

TABLE II.
MP2/6-311+G* Optimized Geometrical Parameters of Conformers of 2-Fluoroglycine.

	I	**II**	**IV**	**V**	**V′**	**VI**	**VII**
C—O	1.349	1.356	1.352	1.356	1.366	1.345	1.351
C—C	1.526	1.540	1.521	1.519	1.526	1.536	1.537
N—C	1.391	1.428	1.399	1.405	1.429	1.396	1.396
H—N	1.009	1.021	1.018	1.018	1.017	1.015	1.016
H—N	1.013	1.018	1.016	1.017	1.017	1.012	1.015
C=O	1.221	1.212	1.219	1.218	1.213	1.217	1.213
O—H	0.982	0.985	0.982	0.981	0.982	0.981	0.981
C—H	1.091	1.095	1.090	1.090	1.100	1.096	1.090
C—F	1.438	1.404	1.443	1.437	1.395	1.449	1.464
C—C—O	111.3	113.2	111.4	110.9	109.8	115.4	115.7
C—C—N	111.8	110.7	109.7	111.0	110.5	111.5	111.4
H—N—C	117.9	111.1	112.2	112.4	111.6	114.2	114.6
H—N—C	116.4	111.8	113.0	112.6	112.2	115.6	113.7
H—N—H	115.5	108.4	111.3	110.6	109.8	112.3	111.3
C—C=O	124.2	123.7	123.9	124.6	125.9	121.7	121.5
H=O=C	107.1	107.4	107.0	107.1	106.8	108.2	108.2
N—C—F	111.9	113.1	113.9	113.6	108.9	111.2	113.0
C—C—F	103.3	108.0	103.7	105.4	107.9	106.0	106.5
H—C—F	104.5	106.5	104.9	105.7	104.9	102.7	104.1
F—C—C=O	−71.5	156.5	−91.2	71.8	169.4	−22.6	11.4
F—C—C =O	107.7	−26.7	87.0	−107.9	−12.6	159.6	−169.4
H—N—C—F	112.7	−50.6	−65.7	−59.9	77.8	−126.1	−64.7
H—N—C—F	−103.5	70.6	61.1	65.7	−158.5	101.3	64.8
H—O—C—C	176.9	−7.6	176.8	−179.3	178.3	9.5	−5.4
N—C—C—O	168.0	32.2	146.8	−51.5	50.4	−143.7	−112.3
N—C—C=O	−12.8	−151.0	−35.0	128.8	−131.7	38.5	66.9
H—N—C—C	−132.0	70.7	50.0	58.6	−163.8	−8.0	55.1
H—N—C=C	11.8	−168.4	176.8	−175.8	−40.1	−140.6	−175.4
N—H···O=C	2.327	—	2.472	—	—	2.384	—
N—H···O—C	—	—	—	2.438	2.287	—	—
N···H—O	—	2.072	—	—	—	—	—
F···H—O	—	—	—	—	—	1.948	1.916
N···H—O	—	—	—	—	—	—	

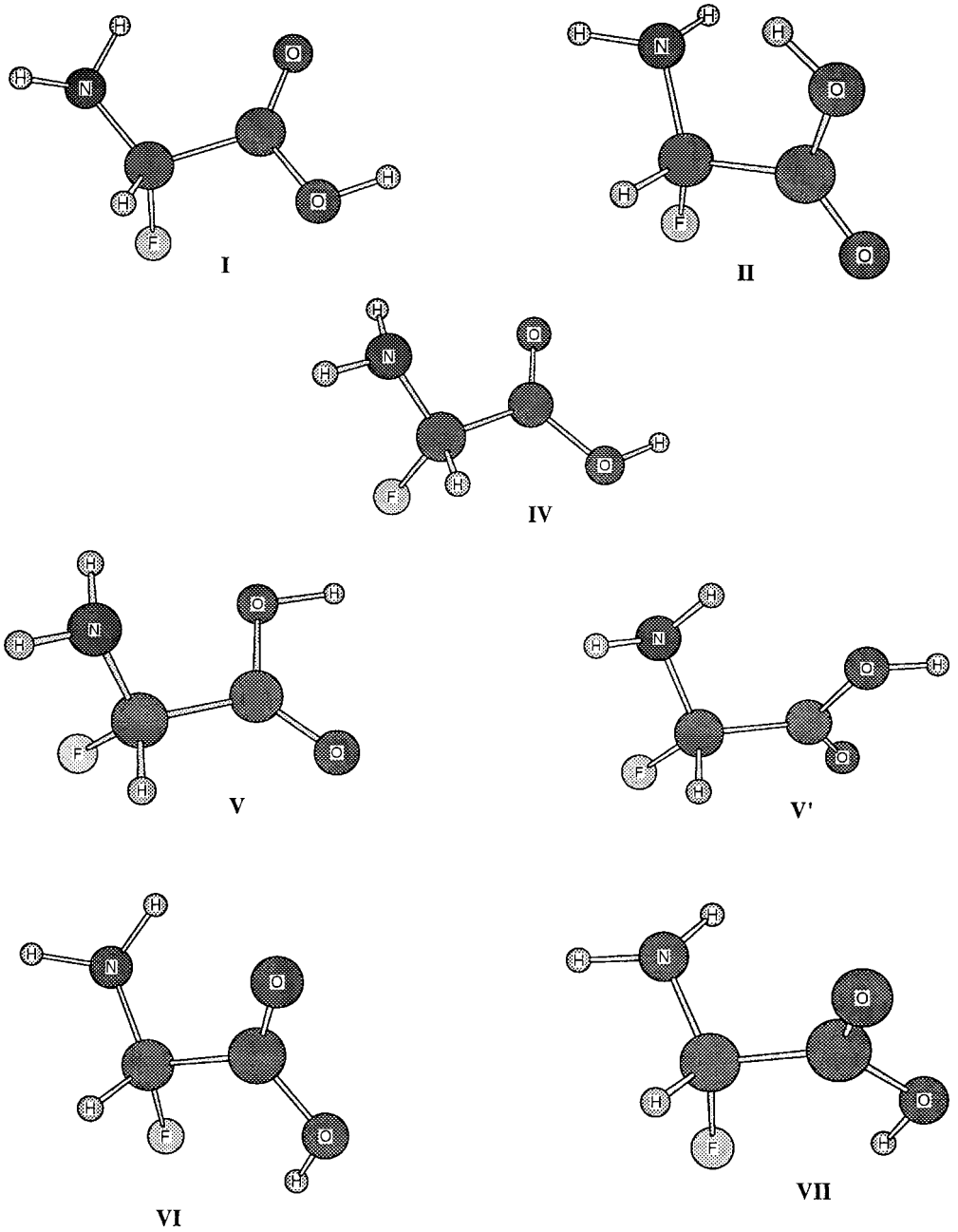

FIGURE 2. MP2/6-311+G* structures of different conformers of 2-fluoroglycine.

for glycine the most stable conformer is one similar to **I**, which is also described as a "stretched out conformer," and a conformer similar to **V** is less stable than **I**. Surprisingly, **V′** is much less stable than **V**, even though **V′** is generated by a slight rotation about the C—N bond. The energy difference between these two conformers, **V** and **V′**, is 25.9 kJ/mol at the MP2 level of theory. The C—N bond is much shorter for the more stable **V** compared to **V′**; the bond lengths for **II** and **V′** are 1.405 and 1.429 Å, respectively. The C—F bond is slightly longer for the more stable **V** than **V′**, and the lengths are 1.443 and 1.437 Å, respectively. The N—C—F bond angle of the more stable conformer is larger and more sp^2-like than that of the least stable conformer; the bond angles of **V** and **V′** are 113.9° and 108.9°, respectively. For conformer **V** the amino lone pair of electrons are antiperiplanar to the C—F bond: the hydrogens are bifurcated about the fluorine; the H_1—N—C—F and H_2—N—C—F dihedral

angles are −59.9° and 65.7°, respectively. For **V′** the amino lone pair of electrons is not antiperiplanar to the C—F bond, and similar dihedrals are 77.8° and −158.5°, respectively.

Conformer **IV**, which is the other stable conformer, is obtained by a 180° rotation of the C—C bond of conformer **V**. From Table II the amino lone pair of electrons of conformer **IV** is also antiperiplanar to the C—F bond; the H—N—C—F dihedrals are −59.9° and 65.7°, which indicates that the amino hydrogens are bifurcated about the fluorine. In addition, it exhibits features similar to conformer **V**: the C—N bond length of **IV** is 1.399 Å, the C—F bond length is 1.443 Å, and the N—C—F bond angle is 113.9°. Conformer **IV** is more stable than conformer **V**; however, two factors may contribute to this difference in stability: conformer **IV** has a slightly smaller dipole moment than conformer **V**, and a stronger hydrogen bond formed to the more basic carbonyl oxygen in **IV** compared to the hydrogen bond formed to the carboxylate OH in **V**. For glycine it is known that the conformer with the smallest dipole moment is also the most stable conformer.[3]

Conformer **II** is capable of an intramolecular hydrogen bond involving the amino lone pair of electrons. Glycine **II** is 14.2 kJ/mol more stable than glycine **I** (Table I) whereas the energy difference for similar conformers of fluoroglycine is 4.7 kJ/mol at the RHF/6-311++G** level (Table I). The relative energy difference between conformers **I** and **II** of fluoroglycine is smaller than that of glycine. The more effective hydrogen bonding, caused from the inductive effect of the electronegative fluorine, may contribute to the relative stability of fluoroglycine **II**, compared to a similar conformer of glycine. Conformer **II′**, which was generated by the rotation about the C—N bond so that the amino electrons were not antiperiplanar to the C—F bond, could not be optimized at basis sets larger than 6-31G*. At the RHF/6-31+G* level it optimized to conformer **VI**.

Conformers **VI** and **VII** are similar to conformer **II**, except that there is a C—C bond rotation that places carboxylic OH out of the reach of hydrogen bonding to the amino lone pair of electrons. This reduction in the hydrogen bond may account for both conformers being less stable than **II**. Conformer **VII** differs from conformer **VI** in that **VII** is generated by the rotation of the C—N bond of **VI** to place the lone pair of electrons antiperiplanar to the C—F bond. The energy difference between **VI** and **VII** is small (4.1 kJ/mol). These conformers are the only conformers that have the acidic OH hydrogen close to the fluorine atom; the nonbonded distances are 1.948 and 1.916 Å for **VI** and **VII**, respectively (Table II). Due to this F···H—O interaction, the C—F bond lengths are longer than expected (1.449 and 1.464 Å). Because this F···H—O distance is well within the van der Waals radii for both atoms, it can be assumed that a F···H—O hydrogen bond is formed and it gives additional stability to **VI** of fluoroglycine, which is not possible for glycine. The relative energy difference between **I** and **VI** (glycine), where such possible interaction is not possible, is 35.2 kJ/mol (at the RHF/6-311++G** level, Table I) whereas this difference for **I** and **VI** (fluoroglycine) is only 6.9 kJ/mol at the same level and 4.7 kJ/mol at the MP2/6-31+G* level. A similar observation is made for both molecules in which a smaller basis set is used: the values for **I** and **VI** at RHF/6-31+G* are 37.4 and 7.0 kJ/mol, respectively.

In conclusion, fluoroglycine is an ideal molecule to study the factors that affect the stability of amino acids that have a very electronegative group on the α position: the stability trend for fluoroglycine is different from that of glycine, which has two hydrogens on the α-carbon. For fluoroglycine conformations that have the amino lone pair of electrons antiperiplanar to the C—F bond, the C—F bond is longer than expected. Also, in conformers in which the carboxylic acid OH group is close to the electronegative fluorine, a F···H hydrogen bond is observed.

References

1. (a) Cao, M.; Newton, S. Q.; Pranata, J.; Schäfer, L. J Mol Struct (Theochem) 1995, 332, 251; (b) Kikuchi, O.; Natsui, T.; Kozaki, T. J Mol Struct (Theochem) 1990, 207, 103; (c) Cassady, C. J.; Carr, S. R.; Zhang, K.; Chung–Phillips, A. J Org Chem 1995, 60, 1704; (d) Sellers, H. L.; Schäfer, L. Chem Phys Lett 1979, 63, 609; (e) McGlone, S. J.; Godfrey, P. D. J Am Chem Soc 1995, 117, 1043; (f) Ramek, M.; Flock, M.; Kelterer, A.-M.; Cheng, V. K. W. J Mol Struct (Theochem) 1992, 276, 61; (g) Ramek, M. J Mol Struct (Theochem) 1990, 208, 301; (h) Gronert, S.; O'Hair, R. A. J Am Chem Soc 1995, 117, 2071; (i) Alsenoy, C. V.; Scarsdale, J. N.; Sellers, H. L.; Schäfer, L. Chem Phys Lett 1981, 80, 124; (j) Kikuchi, O.; Matsuoka, H.; Sawahata, H.; Takahashi, O. J Mol Struct (Theochem) 1994, 305, 79; (k) Schäfer, L.; Siam, K. S.; Klimkowski, V. J.; Alsenoy, C. V.; Kulp–Newton, S. Q. J Mol Struct (Theochem) 1990, 209, 373.
2. (a) Masamura, M. J Mol Struct (Theochem) 1988, 168, 227; (b) Barone, V.; Lelj, F.; Adamo, C. J Chem Phys 1995, 102, 364; (c) Schäfer, L.; Sellers, H. L.; Lovas, F. J.; Suenram, R. D. J Am Chem Soc 1980, 102, 6566; (d) Schäfer, L.; Sellers, H. L. J Am Chem Soc 1978, 100, 7728; (e) Wright, L. R.; Borkman, R. F. J Am Chem Soc 1980, 102, 6207; (f) Vishveshwara, S.; Pople, J. A. J Am Chem Soc 1977, 99, 2422; (g) Yu, D.;

Rauk, A.; Armstrong, D. A. J Am Chem Soc 1995, 117, 1789; (h) Siam, K.; Klimkowski, V. J.; Ewbank, J. D.; Alsenoy, C. V.; Schäfer, L. J Mol Struct (Theochem) 1984, 110, 171; (i) Jensen, J. H.; Gordon, M. S. J Am Chem Soc 1991, 113, 7917.

3. Csaszar, A. J Am Chem Soc 1990, 114, 9568.
4. (a) Godfrey, P. D.; Brown, R. D. J Am Chem Soc 1995, 117, 2019; (b) Suenram, R. D.; Lovas, F. J. J Mol Spectrosc 1978, 72, 372; (c) Brown, R. D.; Godfrey, P. D.; Storey, J. W. V.; Bassez, M.-P. J Chem Soc Chem Commun 1978, 547; (d) Suenram, R. D.; Lovas, F. J. J Am Chem Soc 1980, 102, 7180; (e) Iijima, K.; Tanaka, K.; Onuma, S. J Mol Struct 1991, 246, 257.
5. (a) Karabatsos, G. J.; Fenoglio, D. J. Topics Stereochem 1970, 5, 167; (b) Siam, K. S.; Klimkowski, V. J.; Ewband, J. D.; Schäfer, L.; Alsenoy, C. V. J Comput Chem 1984, 5, 451; (c) Wiberg, K. B.; Murcko, M. A. J Comput Chem 1988, 9, 488.
6. Stabel, A.; Dasaradhi, L.; O'Hagan, D.; Rabe, J. P. Langmuir 1995, 11, 1427.
7. O'Hagan, D.; Rzepa, H. S. Chem Commun 1997, 645.
8. Sanda, M.; Miyano, T.; Iwadare, S.; Williamson, J. M.; Arison, B. H.; Smith, J. L.; Douglas, A. W.; Liesch, J. M.; Inamine, E. J Antibiotics 1986, 39, 259.
9. Kitazume, T.; Tain Lin, J.; Yamazaki, T. Tetrahedron Asymmetry 1991, 2, 253.
10. Schirlin, D.; Ducep, J. B.; Baltzer, S.; Bey, P.; Piriou, F.; Wagner, J.; Hornsperger, J. M.; Heydt, J. G.; Jung, M. J.; Danzin, C.; Weiss, R.; Fischer, J.; Mitschler, A.; DeCain, A. J Chem Soc Perkin Trans 1 1992, 1053.
11. (a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. Tetrahedron 1986, 42, 2101; (b) Bendedtti, E.; Toniolo, C.; Hardy, P.; Brarone, V.; Bavoso, A.; Benedettom, D.; Grimaldi, P.; Francesco, L.; Pavone, V.; Pedone, C.; Bonora, M.; Lingham, I. J Am Chem Soc 1984, 106, 8146; (c) Bonora, M.; Toniolo, C.; Di Biasio, B.; Pavone, V.; Pedone, C.; Beneditte, E.; Lingham, I.; Hardy, P. J Am Chem Soc 1984, 106, 8152; (d) Bosch, R.; Bruckner, B.; Jung, G.; Winter, W. Tetrahedron 1982, 38, 3579; (e) Pavone, V.; Lombardi, A.; Saviano, M.; Di Biasio, B.; Nastri, F.; Fattorusso, R.; Zaccaro, L.; Maglio, O.; Yamada, T.; Omote, Y.; Kuwata, S. Biopolymers 1994, 34, 1595; (f) Li, S.-C.; Deber, C. M. J Peptide Protein Res 1997, 40, 243; (g) Hammer, C. F.; Chandrasegaran, S. J Am Chem Soc 1984, 106, 1543.
12. Pavone, V.; Lombardi, A. A.; D'Auria, G.; Saviano, M.; Nastri, F.; Paolillo, L.; Di Biasio, B.; Pedone, C. Biopolymers 1992, 32, 173–183.
13. Frisch, M. J.; Trucks, G. W.; Head–Cordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian 92; Gaussian, Inc.: Pittsburgh, PA, 1992.